Clinical Applications: Vancomycin

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Introduction

- Renewed interest in 1980's due to MRSA -->Increased understanding of the PK/PD
- Routine monitoring? Trough only?
- Nomogram or PK model?

Nephrotoxicity

- Related to trough > 10mg/L,
- Duration of therapy > 21 days,
- Concurrent nephrotoxic agents
- Older patient...

Nephrotoxicity

- Vancomycin alone
  5% (n=60)
- Vancomycin + aminoglycoside
  22% (n=63)

Rybak et al. JAC 1990;679-87

Ototoxicity

- Peaks > 80 mg/l?
- Concurrent ototoxic agents
- Duration of therapy > 21 days
- Older patient...

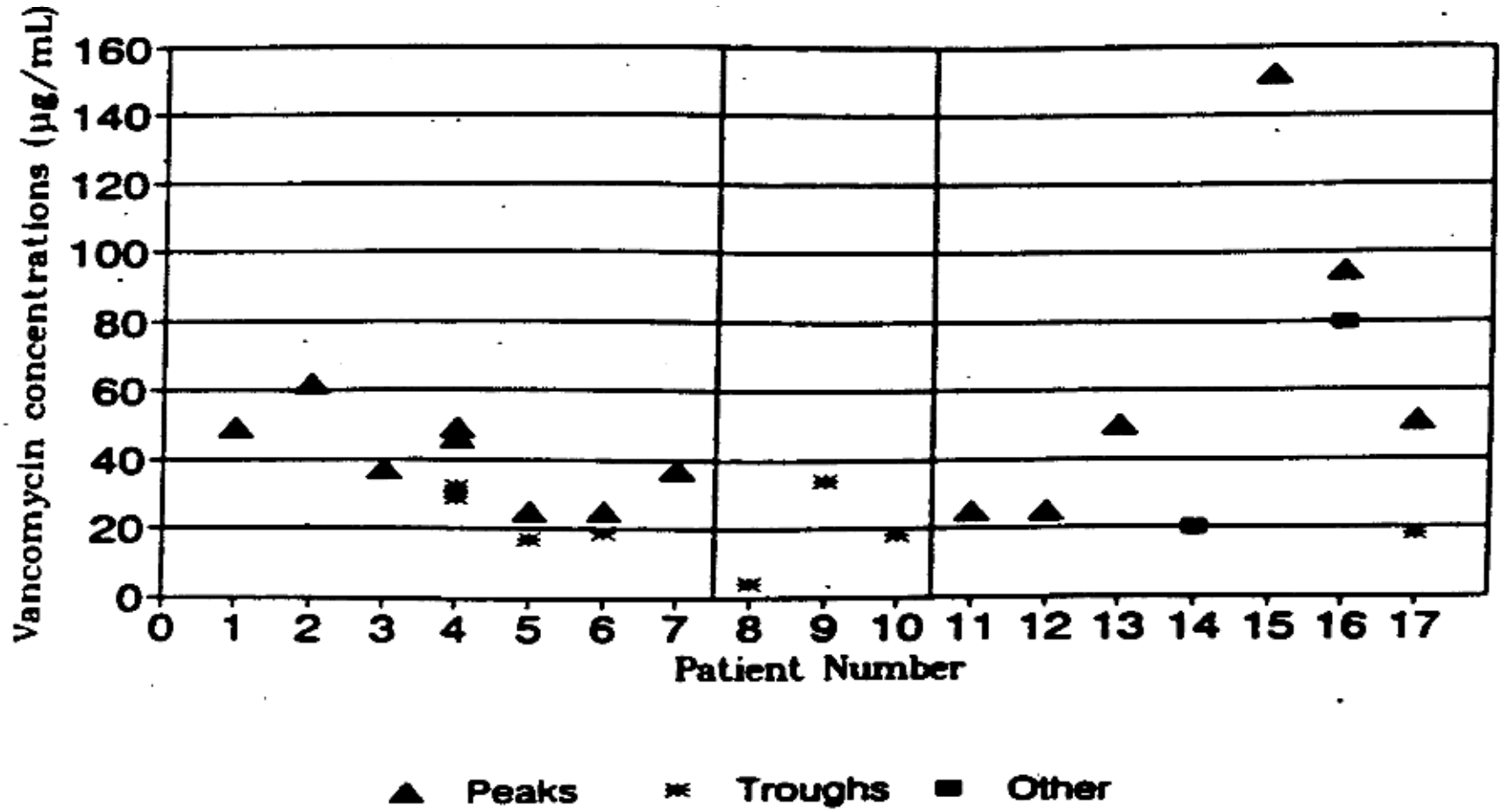

Figure 1. Serum vancomycin concentrations in patients in whom ototoxicity was noted. Patients 1 through 7 either did not use other ototoxic drugs or their use was not reported. Patients 8 through 10 were being treated for meningitis, and patients 11 through 17 received aminoglycosides and/or erythromycin in conjunction with vancomycin. Other = a level that is not a peak or trough.

Pharmacodynamics

- “Concentration-independent killing”
- Maximal activity at 5 x MIC [i.e. 10 mg/L]
- Higher concentrations for deep tissue infections
  - endocarditis, meningitis, osteomyelitis
- Continuous infusion?

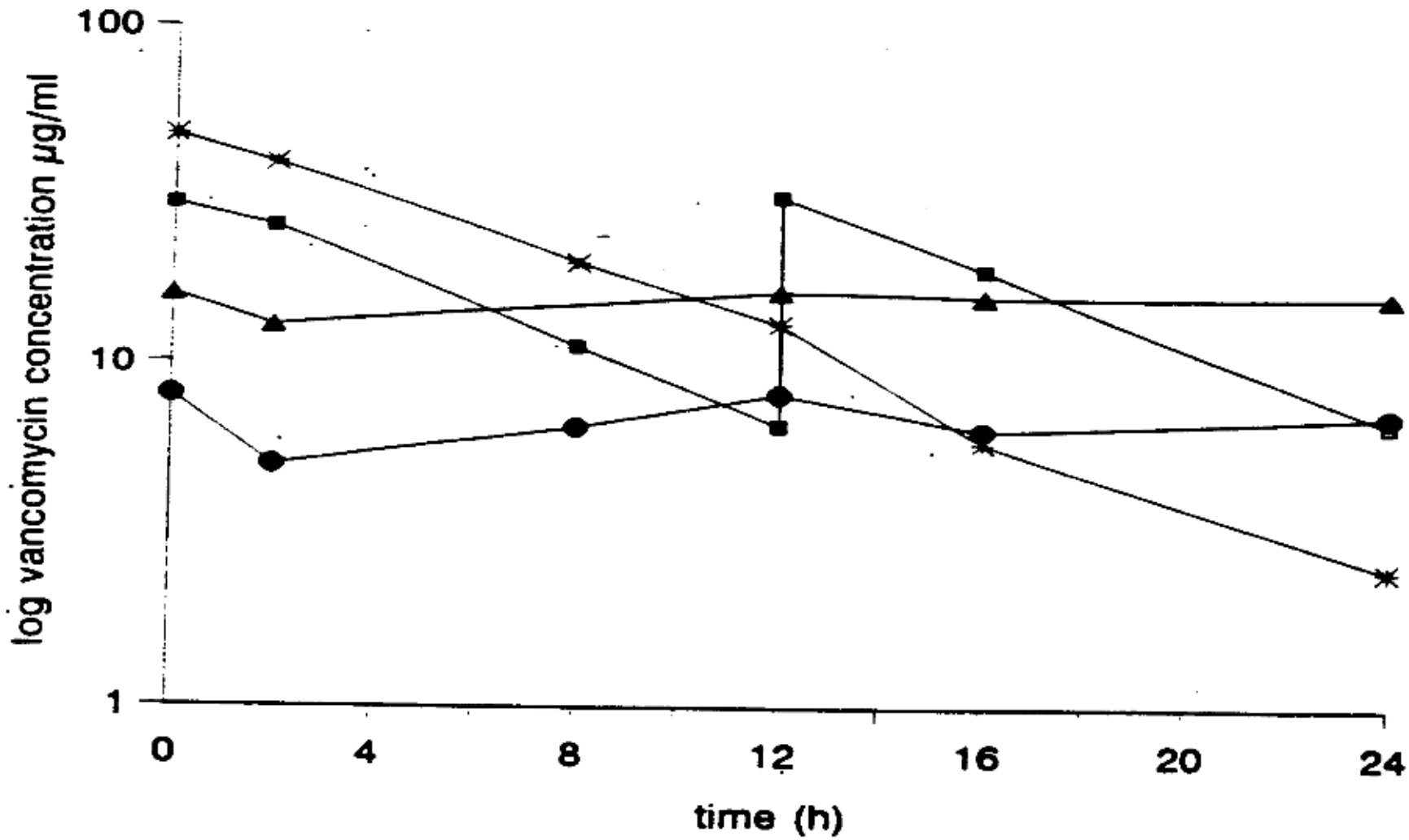

FIG. 1. Concentration-versus-time profile of vancomycin. *, dosing regimen achieving a single peak of 48 µg/ml; ■, dosing regimen to achieve a peak of 30 µg/ml dosed again at 12 h; ▲, dosing regimen achieving a constant concentration of 16.2 µg/ml; ●, dosing regimen achieving a constant concentration of 8 µg/ml.

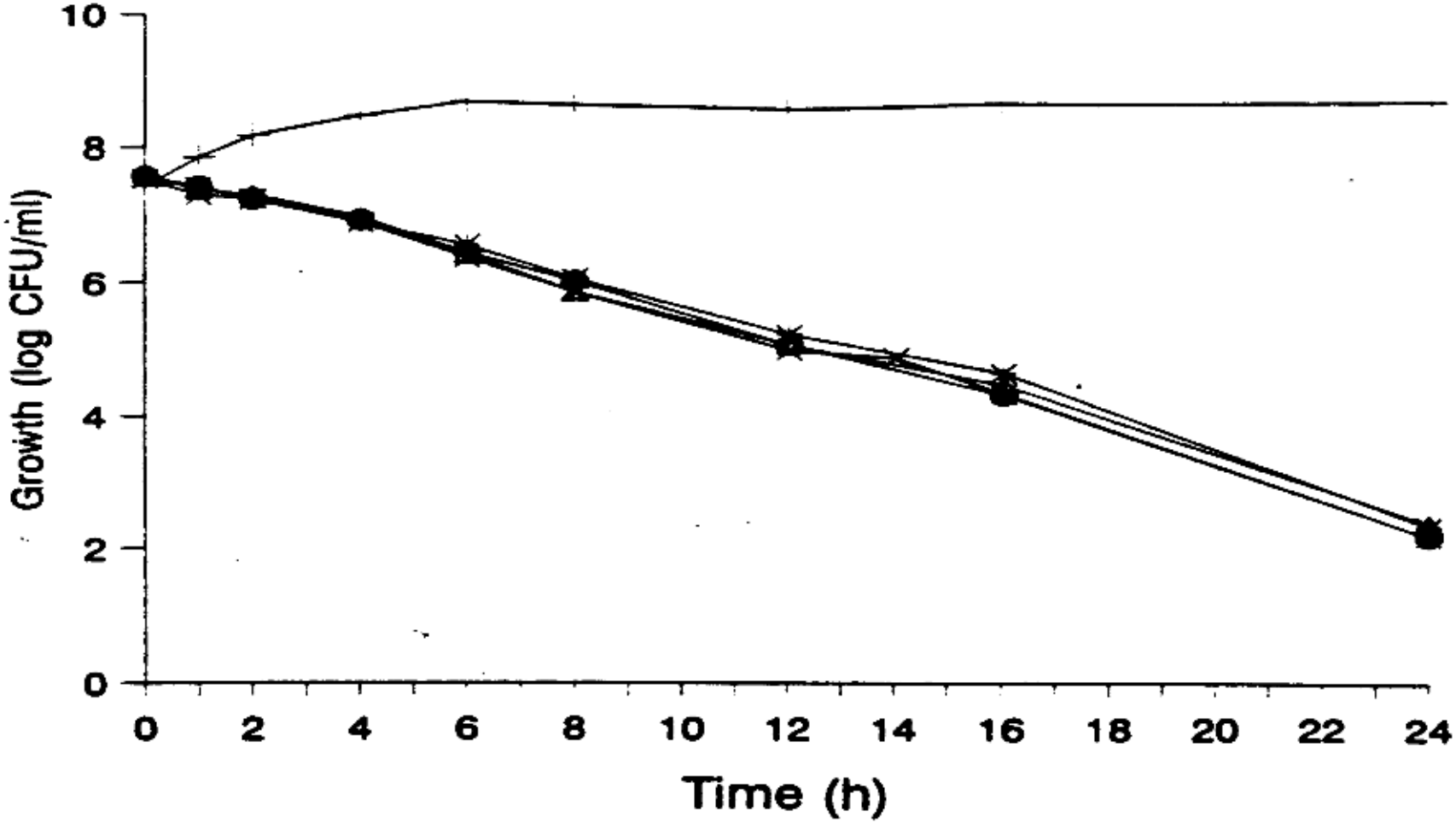

FIG. 2. Antibacterial effects of vancomycin, with different dosing regimens, against *S. aureus* ATCC 29213. +, control bacterial count in the absence of vancomycin; *, dosing regimen achieving a peak of 48 μg/ml; ×, dosing regimen achieving peaks of 30 μg/ml dosed again at 12 h; △, dosing regimen achieving a constant concentration of 16.2 μg/ml; ●, dosing regimen achieving a constant concentration of 8 μg/ml.

Dosing Methods

- Predictive performance: Nomograms vs. PK methods
  - 1 vs 2-compartments
  - Steady state vs non steady state

Predictive Performance

Methods	Peak		Trough	
	ME	MAE	ME	MAE
Moellering	-5.35	8.21	2.26	5.43
Matzke	-5.95	10.5	1.67	5.76
Sawchuk-Zaske	-2.53	4.61	-2.16	2.69
Bayesian	1.73	4.93	-0.67	2.73

Garrelts et al. Clin Pharm 1987;6:795-9

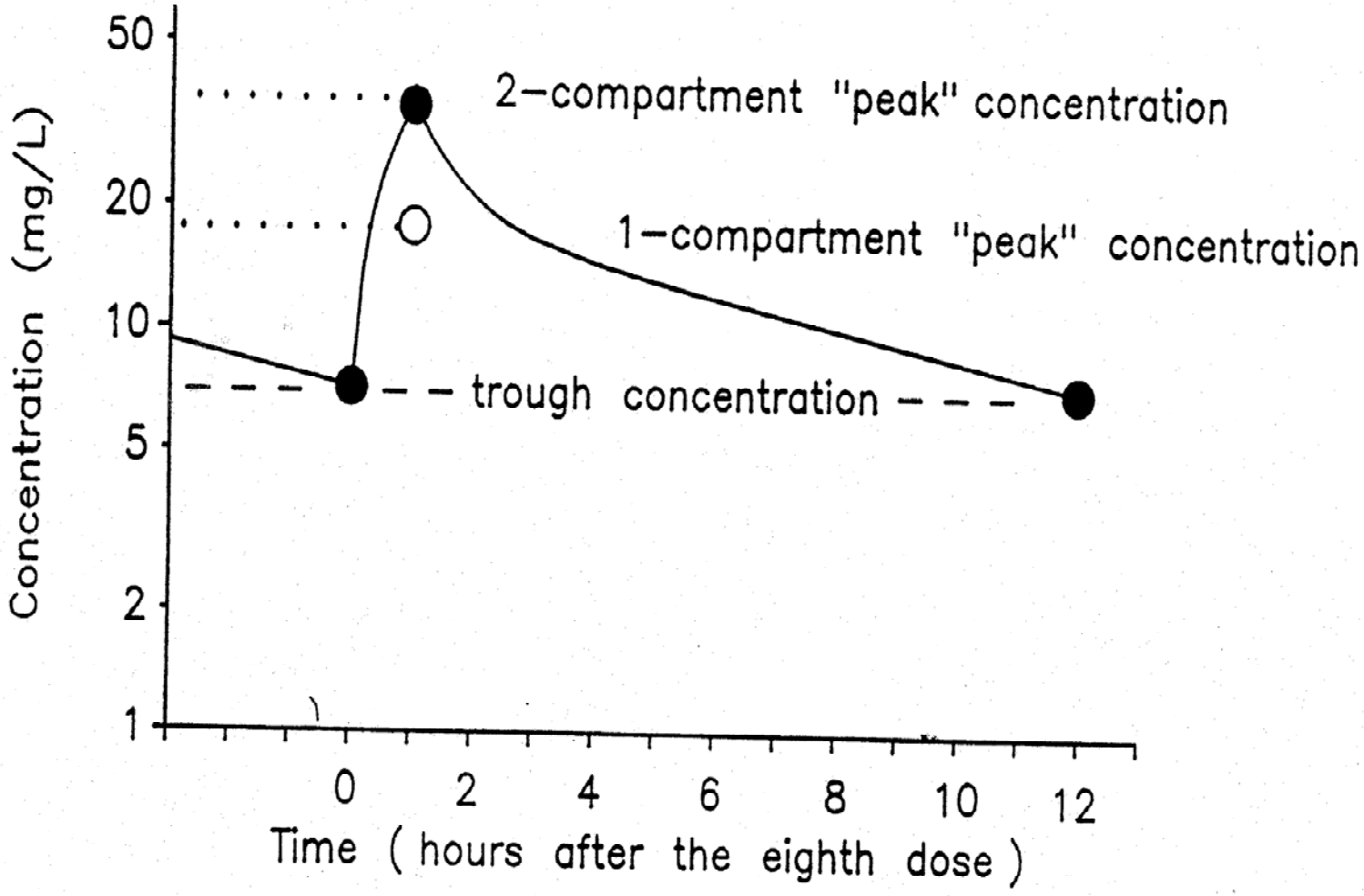

Figure 19–4. Serum concentration–time profile of vancomycin at steady state. Difference between the peak concentrations at the end of infusion for two-compartment model (●) and one-compartment model (O).

Prediction Error (1-compartment model)

Timing	C_{max}	Vd_{ss}	T ½
0.25, 11	29.5 (-18)	0.44 (-37.7)	4.9 (-35.6)
0.5, 11	25.2 (-29.9)	0.54 (-23.3)	5.4 (-28.4)
1, 11	20.5 (-43)	0.72 (2.3)	6.4 (-16.1)
1.5, 11	18.5 (-48.6)	0.84 (19.4)	7.0 (-8.0)
3, 11	17.1 (-52.6)	0.95 (35.1)	7.5 (-0.8)

Two compartment parameters: Cmax 36 mg/L, Vdss 0.7 L/Kg, T1/2 7.6 h

2-Compartment Model

	ME	MAE
LR	-3.2 (16.8)	12.1 (12)
Bayesian	0.0 (4.6)	3.6 (2.7)

Hurst et al. AAC 1990;34:1165-71.

Summary

- Routine Monitoring?
- Target trough
- 2-compartment Bayesian model
  - Peak/Trough required